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10/813,337	03/29/2004	Bill J. Peck	10040506-1	5083

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EXAMINER	
FORMAN, BETTY J	
ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
02/03/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

IPOPS.LEGAL@agilent.com

Office Action Summary	Application No.	Applicant(s)	
	10/813,337	PECK ET AL.	
	Examiner	Art Unit	
	BJ Forman	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-7,10,11,14,16 and 28-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-7, 10-11, 14, 16, 28-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12 November 2008 has been entered.

Status of the Claims

2. This action is in response to papers filed 12 November 2008 in which claims 1, 11 and 30-32 were amended and claims 9 and 15 were canceled. The amendments have been thoroughly reviewed and entered.

The previous rejections in the Office Action dated 12 August 2008, not reiterated below, are withdrawn in view of the amendments. Applicant's arguments have been thoroughly reviewed and are discussed below as they apply to the instant grounds for rejection. New grounds for rejection are discussed.

Claims 1, 3-7, 10-11, 14, 16, 28-37 are under prosecution.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1, 3-7, 10-11, 14, 16, 28, 34-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Perbost (U.S. Patent No. 6,900,048, published 22 November 2001) in view of Anderson et al (U.S. Patent No. 5,186,824, issued 16 February 1993).

Regarding Claims 1, 6-7, Perbost teaches a method of producing an array of at least two different polymers covalently bonded to a surface (Abstract), the method comprising contacting blocked monomer to a first and second location of a surface having functional groups to produce covalently linked monomers, wherein the contacting occurs at a printing station using pulse-jet deposition (print head #210), moving the substrate to a flow cell (flood station #68) for flooding the surface, removing blocking groups of the monomers by sequentially adding a plurality of different liquids at the flow cell station and reiterating the substrate transfer, monomer addition, substrate transfer and sequential liquid application to produce a plurality of different polymers at different locations on the support (Column 10, lines 26-65).

Perbost specifically teaches sequentially step "(d) move substrate 10 back to flood station 68 for oxidation, capping and washing steps over entire substrate" (Column 10, lines 48-50). Thus during a single step "(d)" the substrate is exposed to multiple solutions while at the flood station and therefore sequential addition of a plurality of liquids and replacing the previous liquid. This clearly suggests the presence of stratified liquids because absent a drying step, which Perbost never discusses, sequential application of liquids would contact each other and thereby produce some stratification.

Furthermore, sequential application of liquids via stratified liquid-liquid displacement was well known and routinely practiced in the art of polymer synthesis at the time the claimed invention was made as taught by Anderson et al.

Anderson et al teach a similar method of producing an array of at least two different polymeric ligands (e.g. oligonucleotides synthesized on a solid support (e.g. particle, membrane, disc Column 6, lines 49-56) wherein the method comprises contacting a blocked monomer at first and second locations having functional groups (e.g. cpg supports having the first monomer attached, Column 19, lines 55-58) under conditions sufficient for the monomer to covalently bond to the surface, removing blocking groups to generate a function group and reiterating the steps to produce the array of at least two ligands (Column 19, line 55-Column 20, line 50). Anderson et al further the method wherein the solid supports are exposed to reagents sequentially wherein the reagents are kept separate based on density (Column 5, lines 3-38 and Column 6, lines 13-36) forming a liquid-liquid interface such that the solid support is not exposed to a triple phase interface (Column 12, lines 28-67 and Fig. 2A-2D). Anderson et al disclose the method wherein the functional group generation comprises sequentially contacting at least a portion of the surface with a plurality of liquids (Column 6, line 57-Column 7, line 14) wherein the different liquids include at least an oxidizing liquid, a deblocking liquid, a wash liquid, and a capping liquid (Column 13, line 59-Column 14, line 11 and Column 19, line 55-Column 20, line 50).

Anderson et al further teach the method wherein the sequentially applied liquids have a different density greater than zero (i.e. increasing density, Column 6, line 57-

Column 7, line 14) wherein the sequential contact is performed by displacing a previous liquid with an immediately subsequent liquid produce a stratified liquid interface that moves across the surface (Column 7, line 60-Column 8, line 3, Column 12, lines 28-67 and Fig. 2A-2D).

Anderson et al also teaches that reagent solutions used for polymer synthesis are incompatible (Column 3). To overcome the problems of incompatible reagents, Anderson introduces the reagents at differing densities so as to form a stratified liquid interface moving across the flow cell (Column 5, lines 1-19) thereby eliminating extensive washing between synthesis steps and reducing the waste of expensive reagents (Column 3, lines 54-59).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the fluid displacement synthesis of Anderson et al to the polymer synthesis of Perbost. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success based on the problems using incompatible reagents as taught by Anderson et al (Column 3, lines 54-59) and for the benefit of eliminating the intervening washing thereby reducing waste of time and expensive reagents. One of ordinary skill would have been further motivated to apply the sequential application of synthesis reagents using displacing fluids of differing densities as taught by Anderson to the method of Perbost so as to maintain separation between incompatible reagents with precise control and timing (Anderson, Column 5, lines 1-38).

Regarding Claim 3, Perbost teaches the method different liquids includes an oxidizing liquid and deblocking liquid (Column 8, lines 7-12).

Regarding Claim 4, Perbost teaches the method different liquids includes a washing liquid (Column 8, lines 7-12).

Regarding Claim 5, Perbost teaches the method different liquids includes a capping liquid (Column 8, lines 7-12 and Column 10, lines 48-50).

Regarding Claims 6-7, Perbost teaches the different liquids, which Anderson et al defines the sequentially applied liquids have a different density greater than zero (i.e. increasing density, Column 6, line 57-Column 7, line 14).

Regarding Claim 10-11, 14 Anderson et al disclose a method of producing an array of at least two different polymeric ligands (e.g. oligonucleotides synthesized on control pore glass, the two different sequences being e.g. product and failed sequences, Column 20, lines 10-25).

Anderson et al disclose the method comprising contacting a blocked monomer at first and second locations having functional groups (e.g. cpg supports having the first monomer attached, Column 19, lines 55-58) under conditions sufficient for the monomer to covalently bond to the surface, removing blocking groups to generate a function group and reiterating the steps to produce the array of at least two ligands (Column 19, line 55-Column 20, line 50). Anderson et al teach the method wherein the solid supports are exposed to reagents sequentially wherein the reagents are kept separate based on density (Column 5, lines 3-38 and Column 6, lines 13-36) forming a liquid-

liquid interface such that the solid support is not exposed to a triple phase interface (Column 12, lines 28-67 and Fig. 2A-2D).

Anderson et al further teach the method wherein the flow rate is controlled and monitored during passage of reagents (Column 5, lines 25-27; Column 14, lines 44-53 21) and further teach that it is important to control the flow rate because some synthesis steps take more or less time than other steps and because reagent waste resulting from excess use of reagents is expensive (Column 21, lines 30-65) but they are silent regarding specific flow rates. However, the reference clearly suggests that the flow rate is adjusted to maximize reagents and synthetic step. Therefore, It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to adjust the flow rate during the synthesis steps of Anderson to obtain optimal flow rates (e.g. about 1-20 cm/x). One of ordinary skill in the art would have been motivated to do adjust the flow rate so as to maximize syntheses reaction with minimal waste of reagents as desired by Anderson et al (Column 21, lines 30-65).

Regarding Claim 16, Perbost teaches the method different liquids includes a capping liquid contacting the surface between the oxidizing and deblocking liquid (Column 8, lines 7-12).

Regarding Claim 28, Perbost teaches the method wherein the substrate is planar (Column 12, line 17-18).

Regarding Claims 34-35 Perbost teaches the method wherein at least 10 different polymers are produced (Column 7, lines 1-3).

Regarding Claim 36, Perbost teaches the method wherein the substrate is moved using a transfer element (Column 10, line 31).

5. Claims 1, 3-4, 28, 34-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bass et al (U.S. Patent No. 6,420,180, issued 16 July 2002) in view of Anderson et al (U.S. Patent No. 5,186,824, issued 16 February 1993).

Regarding Claim 1, Bass et al disclose a method of producing an array of at least two different polymers covalently bonded to a surface (Column 7, lines 20-24), the method comprising contacting blocked monomer to a first and second location of a surface having functional groups (Column 13, lines 35-57), to produce covalently linked monomers, removing blocking groups of the monomers without exposing the surface to triple phase interphase gas, solid liquid (e.g. all additional steps are performed in flood station #68, Column 7, line 20-Column 9, line 9) and reiterating the steps to produce an array having at least two polymers at the first and second locations. Bass et al teach the method wherein the functional group generation step comprises sequentially contacting at least a portion of the surface with different liquids (Column 8, lines 57-Column 9, line 9). Bass et al teach the method wherein the functional group generation step occurs in a flow cell i.e. flood station (Column 8, lines 57-Column 9, line 9). Bass et al teach the method wherein the monomers are deposited using a pulse-jet (Column 4, line 44-Column 8-Column 9, line 9). Bass further teach the method wherein the

substrate is moved between the flow cell and monomer print station for monomer addition via pulse jet (Column 9).

Bass et al specifically teach sequentially contacting at least a portion of the surface with different liquids (Column 8, lines 57-Column 9, line 9) but does not specifically teach that the sequentially applied liquids displace previous liquid.

However sequential application of liquids via liquid-liquid displacement was well known and routinely practiced in the art of polymer synthesis at the time the claimed invention was made as taught by Anderson et al.

Anderson et al teach a similar method of producing an array of at least two different polymeric ligands (e.g. oligonucleotides synthesized on a solid support (e.g. particle, membrane, disc Column 6, lines 49-56) wherein the method comprises contacting a blocked monomer at first and second locations having functional groups (e.g. cpg supports having the first monomer attached, Column 19, lines 55-58) under conditions sufficient for the monomer to covalently bond to the surface, removing blocking groups to generate a function group and reiterating the steps to produce the array of at least two ligands (Column 19, line 55-Column 20, line 50). Anderson et al further the method wherein the solid supports are exposed to reagents sequentially wherein the reagents are kept separate based on density (Column 5, lines 3-38 and Column 6, lines 13-36) forming a liquid-liquid interface such that the solid support is not exposed to a triple phase interface (Column 12, lines 28-67 and Fig. 2A-2D). Anderson et al disclose the method wherein the functional group generation comprises sequentially contacting at least a portion of the surface with a plurality of liquids

(Column 6, line 57-Column 7, line 14) wherein the different liquids include at least an oxidizing liquid, a deblocking liquid, a wash liquid, and a capping liquid (Column 13, line 59-Column 14, line 11 and Column 19, line 55-Column 20, line 50).

Anderson et al further teach the method wherein the sequentially applied liquids have a different density greater than zero (i.e. increasing density, Column 6, line 57-Column 7, line 14) wherein the sequential contact is performed by displacing a previous liquid with an immediately subsequent liquid produce a stratified liquid interface that moves across the surface (Column 7, line 60-Column 8, line 3, Column 12, lines 28-67 and Fig. 2A-2D).

Anderson et al also teaches that reagent solutions used for polymer synthesis are incompatible (Column 3). To overcome the problems of incompatible reagents, Anderson introduces the reagents at differing densities so as to form a stratified liquid interface moving across the flow cell (Column 5, lines 1-19) thereby eliminating extensive washing between synthesis steps and reducing the waste of expensive reagents (Column 3, lines 54-59).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the fluid displacement synthesis of Anderson et al to the polymer synthesis of Bass et al. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success based on the problems using incompatible reagents as taught by Anderson et al (Column 3, lines 54-59) and for the benefit of eliminating the intervening washing thereby reducing waste of time and expensive reagents. One of ordinary skill would have been further motivated to apply

the sequential application of synthesis reagents using displacing fluids of differing densities as taught by Anderson to the method of Bass so as to maintain separation between incompatible reagents with precise control and timing (Anderson, Column 5, lines 1-38).

Regarding Claim 3, Bass et al teach the method different liquids includes an oxidizing liquid and deblocking liquid (Column 8, lines 57-Column 9, line 9).

Regarding Claim 4, Bass et al teach the method different liquids includes a washing liquid (Column 8, lines 57-Column 9, line 9).

Regarding Claim 28, Bass et al teach the method wherein the substrate is planar (Fig. 1).

Regarding Claims 34-35, Bass et al teach the method wherein at least 10 different polymers are produced (Fig. 1-2).

Regarding Claim 36-37, Bass et al teach the method wherein the substrate is moved using a robotic arm (i.e. transporter #60, Fig. 6).

Response to Arguments

6. Applicant asserts that Bass'180 in view of Anderson would not lead one skilled in the art to combine the elements as suggested by the office without hindsight reasoning.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does

not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicant asserts that the teaching of Bass'180 relates to a method of pulse jetting reagents onto a substrate and exposing the substrate to certain fluids in a flood station. Applicant further asserts that Bass is completely silent regarding displacing a previous fluid with a subsequent fluid as claimed. Applicant argues that the methods of Bass and Anderson are very different in that Anderson teaches batch synthesis on glass beads within a rotor while Bass teaches synthesis at discrete addressable locations. From this Applicant argues that the methods are not combinable. The argument has been considered but is not found persuasive. As stated above, both Bass and Anderson teach methods of oligonucleotide synthesis via monomer addition using the same reagents. Anderson et al further teaches that reagent solutions used for polymer synthesis are incompatible (Column 3). To overcome the problems of incompatible reagents, Anderson introduces the reagents at differing densities so as to form a stratified liquid interface moving across the flow cell (Column 5, lines 1-19) thereby eliminating extensive washing between synthesis steps and reducing the waste of expensive reagents (Column 3, lines 54-59). It is maintained that Anderson teaches oligonucleotide synthesis via application of stratified reagents and it is maintained that Anderson provides the reasoning and motivation for using the stratified reagents in the method of Bass.

Applicant further argues that the combination of Bass and Anderson would be inoperable because Anderson uses a rotor and introduces the reagents during rotation. Applicant asserts that combining such rotation to the in situ fabrication of Bass would result in array damage dues to centrifugal force within the rotor. The argument has been considered but is not found persuasive. Applicant has not provided any evidence or inoperability. As such, the assertion is deemed unsupported arguments of counsel.

> The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. (see (MPEP 716.01(c).

Furthermore, as noted in the Advisory Action, Anderson is not limited to synthesis within a rotor because the reference teaches the method is also applicable to a "column at rest" (Column 5 and Abstract). Applicant notes the citation of a column at rest, but argues that Anderson only mentions the column once, while the remaining reference is devoted to teaching rotor rotation. The argument is noted but it is maintained that Anderson specifically teaches the optional method (see also Abstract). In addition, Bass is specifically interested in applying multiple & sequential reagents during the in situ synthesis using the flood station (Column 9, lines 1-9). Bass teaches a single flood station for adding multiple and sequential reagents. This clearly suggests that the reagents are added sequentially so as to displace the previous reagent.

Anderson teaches sequential reagent addition and teaches the advantages of doing so. It is maintained that the combination of Bass and Anderson obviates the instantly claimed invention.

Finally, Bass and Anderson are both interesting in synthesizing a plurality of oligonucleotides via monomer phosphoramidite chemistry. It would have been obvious to one of ordinary skill to advantageous elements of Anderson to the method of Bass based on the explicit need and advantages taught by Anderson i.e. to overcome the problems of incompatible reagents, Anderson introduces the reagents at differing densities so as to form a stratified liquid interface moving across the flow cell (Column 5, lines 1-19) thereby eliminating extensive washing between synthesis steps and reducing the waste of expensive reagents (Column 3, lines 54-59).

The rejection is maintained.

7. Claims 1, 3-7, 10-11, 14, 16, 28, 34-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bass (B) (U.S. Patent No. 6,440,669, issued 27 August 2002) in view of Anderson et al (U.S. Patent No. 5,186,824, issued 16 February 1993).

Regarding Claims 1, 6-7, Bass (B) discloses a method of producing an array of at least two different polymers covalently bonded to a surface (Column 10, lines 59-67), the method comprising contacting blocked monomer to a first and second location of a surface having functional groups to produce covalently linked monomers (Column 10, lines 24-67), wherein the contacting occurs at a printing station (platform #32), moving

the substrate to a flow cell (stage #41 for flooding the surface, Column 11, lines 43-50) removing blocking groups of the monomers and sequentially adding a plurality of different liquids at the flow cell station (Column 16, lines 7-63) and reiterating the substrate transfer, monomer addition, substrate transfer and sequential liquid application to produce a plurality of different polymers at different locations on the support (Column 8, lines 8-31).

Bass (B) specifically teaches sequentially contacting at least a portion of the surface with different liquids (Column 16, lines 7-63) but does not specifically teach that the sequentially applied liquids displace previous liquid.

However sequential application of liquids via liquid-liquid displacement was well known and routinely practiced in the art of polymer synthesis at the time the claimed invention was made as taught by Anderson et al.

Anderson et al teach a similar method of producing an array of at least two different polymeric ligands (e.g. oligonucleotides synthesized on a solid support (e.g. particle, membrane, disc Column 6, lines 49-56) wherein the method comprises contacting a blocked monomer at first and second locations having functional groups (e.g. cpg supports having the first monomer attached, Column 19, lines 55-58) under conditions sufficient for the monomer to covalently bond to the surface, removing blocking groups to generate a function group and reiterating the steps to produce the array of at least two ligands (Column 19, line 55-Column 20, line 50). Anderson et al further the method wherein the solid supports are exposed to reagents sequentially wherein the reagents are kept separate based on density (Column 5, lines 3-38 and

Column 6, lines 13-36) forming a liquid-liquid interface such that the solid support is not exposed to a triple phase interface (Column 12, lines 28-67 and Fig. 2A-2D). Anderson et al disclose the method wherein the functional group generation comprises sequentially contacting at least a portion of the surface with a plurality of liquids (Column 6, line 57-Column 7, line 14) wherein the different liquids include at least an oxidizing liquid, a deblocking liquid, a wash liquid, and a capping liquid (Column 13, line 59-Column 14, line 11 and Column 19, line 55-Column 20, line 50).

Anderson et al further teach the method wherein the sequentially applied liquids have a different density greater than zero (i.e. increasing density, Column 6, line 57-Column 7, line 14) wherein the sequential contact is performed by displacing a previous liquid with an immediately subsequent liquid produce a stratified liquid interface that moves across the surface (Column 7, line 60-Column 8, line 3, Column 12, lines 28-67 and Fig. 2A-2D).

Anderson et al also teaches that reagent solutions used for polymer synthesis are incompatible (Column 3). To overcome the problems of incompatible reagents, Anderson introduces the reagents at differing densities so as to form a stratified liquid interface moving across the flow cell (Column 5, lines 1-19) thereby eliminating extensive washing between synthesis steps and reducing the waste of expensive reagents (Column 3, lines 54-59).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the fluid displacement synthesis of Anderson et al to the polymer synthesis of Bass et al. One of ordinary skill in the art would have been

motivated to do so with a reasonable expectation of success based on the problems using incompatible reagents as taught by Anderson et al (Column 3, lines 54-59) and for the benefit of eliminating the intervening washing thereby reducing waste of time and expensive reagents. One of ordinary skill would have been further motivated to apply the sequential application of synthesis reagents using displacing fluids of differing densities as taught by Anderson to the method of Bass so as to maintain separation between incompatible reagents with precise control and timing (Anderson, Column 5, lines 1-38).

Regarding Claim 3, Bass (B) teaches the method different liquids includes an oxidizing liquid and deblocking liquid (Column 10, lines 42-58 and Column 16, lines 7-63).

Regarding Claim 4, Bass (B) teaches the method different liquids includes a washing liquid (Column 10, lines 42-58 and Column 16, lines 7-63).

Regarding Claim 5, Bass (B) teaches the method different liquids includes a capping liquid (Column 10, lines 42-58 and Column 16, lines 7-63).

Regarding Claims 6-7, Anderson et al further teach the method wherein the sequentially applied liquids have a different density greater than zero (i.e. increasing density, Column 6, line 57-Column 7, line 14).

Regarding Claim 10-11, 14 Anderson et al disclose a method of producing an array of at least two different polymeric ligands (e.g. oligonucleotides synthesized on control pore glass, the two different sequences being e.g. product and failed sequences, Column 20, lines 10-25).

Anderson et al disclose the method comprising contacting a blocked monomer at first and second locations having functional groups (e.g. cpg supports having the first monomer attached, Column 19, lines 55-58) under conditions sufficient for the monomer to covalently bond to the surface, removing blocking groups to generate a function group and reiterating the steps to produce the array of at least two ligands (Column 19, line 55-Column 20, line 50). Anderson et al teach the method wherein the solid supports are exposed to reagents sequentially wherein the reagents are kept separate based on density (Column 5, lines 3-38 and Column 6, lines 13-36) forming a liquid-liquid interface such that the solid support is not exposed to a triple phase interface (Column 12, lines 28-67 and Fig. 2A-2D).

Anderson et al further teach the method wherein the flow rate is controlled and monitored during passage of reagents (Column 5, lines 25-27; Column 14, lines 44-53 21) and further teach that it is important to control the flow rate because some synthesis steps take more or less time than other steps and because reagent waste resulting from excess use of reagents is expensive (Column 21, lines 30-65) but they are silent regarding specific flow rates. However, the reference clearly suggests that the flow rate is adjusted to maximize reagents and synthetic step. Therefore, It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to adjust the flow rate during the synthesis steps of Anderson to obtain optimal flow rates (e.g. about 1-20 cm/x). One of ordinary skill in the art would have been motivated to do adjust the flow rate so as to maximize syntheses reaction with minimal waste of reagents as desired by Anderson et al (Column 21, lines 30-65).

Regarding Claim 16, Bass (B) teaches the method different liquids includes a capping liquid contacting the surface between the oxidizing and deblocking liquid (Column 10, lines 42-58 and Column 16, lines 7-63).

Regarding Claim 28, Bass (B) teaches the method wherein the substrate is planar (Fig. 1).

Regarding Claims 34-36 Bass (B) teaches the method wherein at least 10 different polymers are produced (Column 8, lines 22-25).

Regarding Claim 36-37, Bass (B) teaches the method wherein the substrate is moved using a robotic arm (#36b, Fig. 2).

Response to Arguments

8. Applicant asserts that Bass'669 in view of Anderson would not lead one skilled in the art to combine the elements. Applicant reasserts the reasoning discussed above regarding the Bass'180 reference. The reasoning has been thoroughly reviewed and in not found persuasive as discussed above.

Applicant further argues that the art of array synthesis at the time of filing only teaches drying steps between exposures to different fluids. From this, Applicant asserts the combination of Bass and Anderson would not have been obvious. The argument has been considered but is not found persuasive. Bass is specifically interested in adding multiple and subsequent reagents to the substrate without moving the substrate from the flow cell (see column 16, lines 43-51 below).

> Following the washing step and while substrate wafer 36 remains at second platform 33, ultrasonic fluid ejection device 44 is activated to dispense a deblocking reagent to

> uniformly coat the surface of substrate wafer 36. Again, excess liquid and reagents may be removed from the surface of wafer 36 and, while substrate wafer 36 remains at second platform 33, ultrasonic fluid ejection device 44 is activated to dispense a wash liquid to wash the surface of wafer 36.

It is maintained that the combination of Bass and Anderson obviates the instant invention.

Applicant argues that Anderson does not suggest the flow rate and/or sensing reagent movement as recited in Claims 10 and 11. As noted above, Anderson specifically teaches carefully monitored and controlled flow rate Column 5, lines 25-27 and Column 9, line 66-Column 10, line 4) and further teach that it is important to control the flow rate because some synthesis steps take more or less time than other steps and because reagent waste resulting from excess use of reagents is expensive (Column 21, lines 30-65) but they are silent regarding specific flow rates. However, the reference clearly suggests that the flow rate is adjusted to maximize reagents and synthetic step. Therefore, It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to adjust the flow rate during the synthesis steps of Anderson to obtain optimal flow rates (e.g. about 1-20 cm/x). One of ordinary skill in the art would have been motivated to do adjust the flow rate so as to maximize syntheses reaction with minimal waste of reagents as desired by Anderson et al (Column 21, lines 30-65). Furthermore, it is noted that *In re Aller*, 220 F.2d 454,456, 105 USPQ 233,235 states where the general conditions of a claim are disclosed in the

prior art, it is not inventive to discover the optimum by routine experimentation. It is maintained that the flow rates as claimed would have been an optimization of the controlled flow as taught by Anderson.

The rejection is maintained.

9. Claims 29-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bass (B) (U.S. Patent No. 6,440,669, issued 27 August 2002) in view of Anderson et al (U.S. Patent No. 5,186,824, issued 16 February 1993) as applied to Claim 1 above and further in view of Goldberg (U.S. Patent No. 5,959,098, issued 28 September 1999).

Regarding Claim 29-33, Bass and Anderson teach all the elements of Claim 1 as discussed above but are silent regarding the plane of the flow cell or environment. However, flow cells vertical to the horizon (i.e. greater than 75 degrees) were well know and routinely practiced in the art of polymer synthesis as taught by Goldberg (Fig. 6). Goldberg further teaches this vertical alignment is preferred because it improves fluid circulations and facilitates removal of bubbles (Column 16, lines 13-21). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the vertical flow cell arrangement of Goldberg to the flow cell of Bass. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success and for the added benefit of improved fluid circulation and facilitated removal of bubbles as desired in the art (Goldberg, Column 16, lines 13-21).

Response to Arguments

10. Applicant asserts that Goldberg does not cure the deficiencies of Bass and Anderson and therefore cannot obviate the invention of Claims 29-33. The argument has been considered but is not found persuasive because Bass and Anderson are not deed deficient.

The rejection is maintained.

Conclusion

11. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (571) 272-0741. The examiner can normally be reached on 6:00 TO 3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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